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Mitochondrial DNA and Disease: Areview

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Abstract

Mitochondria are organelles responsible for converting energy into a usable form for cellular metabolic activities. These organelles have their own DNA. Mutations in mitochondrial DNA (mtDNA) are frequent despite Its limited number of genes. Molecular genetics diagnostics enables the examination of DNA in many fields, like infectiology, cancer, and genetics of people. It is essential to identify abnormalities in mitochondrial DNA in patients since these mutations directly affect mitochondrial metabolism and may contribute to various illnesses. The mtDNA found in every human cell is a limited and significant source of harmful mutations and rearrangements. This review provides a concise overview of the unique principles of mitochondrial genetics, including maternal inheritance, mitotic segregation, heteroplasmy, and the threshold effect. It emphasizes the relatively common occurrence of medical conditions associated with mitochondrial DNA (mtDNA) and discusses recent discoveries of pathogenic mutations, with a particular focus on mutations that impact protein-coding genes. Next, we go into more contentious topics, such as the functional or pathological significance of mtDNA haplotypes, the disease-causing potential of homoplasmic mutations, and the mostly unknown mechanisms behind mtDNA mutations.

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1. Introduction

Mitochondria are the organelles in eukaryotic cells responsible for converting fuels into Adenosine triphosphate ATP by oxidative phosphorylation to provide energy for cellular metabolism. Mitochondria possess a double membrane. The membrane on the outside of the mitochondrion acts as a barrier between the mitochondrion and the cytoplasm. The inner layer of the membrane is folded to create cristae, which extend into and delineate the matrix of the organelle. The five complexes of enzymes within the phosphate oxidation system are situated inside the mitochondrial inner membrane. Mitochondria possess their genetic material, known as mtDNA, situated in the mitochondrial matrix. Every organelle in cells of mammals typically has several identical copies of mtDNA [1]. Mitochondria were formerly believed to be proteobacteria had been assimilated into a eukaryotic cell by endocytosis. The mitochondria's unique genome and genetic code, distinct from nuclear DNA, may be attributed to their endosymbiotic origin. During evolution, this DNA likely lost the majority of its genes, which were then integrated into the nuclear DNA [2]. The number of cells or gene contents differs across different species. The human mitochondrial genome comprises around 1% of the total cellular DNA and exists in around one thousand to ten thousand copies of each cell. Each mitochondrion typically contains between 5 or 10 copies. The mitochondria are regarded as the cell's energy source as they generate the majority of the cell's energy through oxidative phosphorylation, producing ATP by linking the respiratory chain with ATP synthase. Enzyme complexes involved in these activities

consist of components that are generated by both nuclear and mtDNA. Over 200 mutations in mtDNA have been documented. Many mitochondrial DNA problems exhibit heteroplasmy, with increased levels of heteroplasmy associated with various illnesses. Some mtDNA illnesses exhibit complete homoplasmy for harmful mutations. A 100% homoplasmic mtDNA mutations may lead to severe consequences, including premature death [3]. A wide range of illnesses known as mitochondrial encephalomyopathies are caused by structural, biochemical, or genetic abnormalities in the mitochondria. Physicians in several areas encounter patients with mitochondrial disorders because almost all organ systems can be affected by mitochondrial dysfunction [4]. While mitochondrial illnesses might vary in their clinical presentation and disease development, they often exhibit significant systemic consequences that contribute to their death. Since the identification of the first DNA in mitochondria mutations in 1988, our comprehension of the role of mitochondrial DNA in certain illnesses has quickly evolved [5]. These mutations have been identified in several disorders, and studies are underway to establish the harmful impact of accumulating mitochondria DNA damage in numerous common illnesses that appear later [6]. The circular, double-stranded, 16,569 nucleotide pairs (bps) human mtDNA as shown in figure 1 is home to 37 genes, including 22 tRNA genes, 2 rRNA genes, and 13 structural genes that code for components of the mitochondrial respiratory chain [7,8], the "business end" of oxidative metabolism where ATP is produced [9].The electron transport chain, which is comprised of four multimeric complexes (I to IV) and two small electron carriers, coenzyme Q (also known as ubiquinone) and cytochrome c, is a sequence of protein complexes embedded in the inner mitochondrial membrane that carry reducing equivalents produced in the Krebs cycle and in the ß-oxidation spirals (Figure 2). Protons are pumped from the mitochondrial matrix into the area between the inner and outer mitochondrial membranes using the energy produced by the electron transport chain's reactions [10]. The tRNAs required for the expression of these genes are shown in figure 1 [11]. The light (L) chain, rich in C, encodes both short and big Ribosomal RNA (rRNAs), 12 peptides, and 14 Transfer ribonucleic acid (tRNAs) [12]. mtDNA is particularly at risk for mutation due to its weak DNA repair mechanism, sensitivity to damage caused by reactive oxygen species (ROS) inside the mitochondria, and the lack of protective histone proteins [13]. Genetic alterations in mtDNA are responsible for the deterioration of energy production in several disorders and during the natural aging phenomenon [14]. Several mutations or deletions in the tRNA genes of mtDNA might disable one or more tRNA genes that are necessary for protein synthesis. These disabling mutations, referred to as syn$^-$ mutations and shown as x in Figure 2 [15, 16]. Figure 2 displays several types of mtDNAs with distinct genetic compositions (heteroplasmy) and nuclear DNAs (nDNAs) inside a heterokaryon [17]. Due to the presence of the mitochondrial membrane, tRNAs are restricted to the inside of mitochondria. When cells A or B have a fusogenic protein, mitochondria A and B undergo fusion to become mitochondria A or B. In the mitochondria A or B that are produced, two distinct syn mutations may be restored by replacing the remaining wildtype tRNAs A and B [18]. This substitution restores both translation and cellular functioning (Figure 2 top right) [19, 20].

2. Structures and Function of Mitochondria

In order to understand mitochondrial illness, it is imperative to examine the unique attributes of mitochondrial DNA. Mitochondria generate ATP via oxidative phosphorylation, which serves as the energy source for cellular activities [21]. The extrachromosomal DNA present in these organelles has distinct characteristics from the DNA found within the nucleus, as shown in figure 1 [22]. Human mitochondrial DNA, also known as "the other human genome," is a circular molecule with two strands. It contains 24 structural RNAs, which include 22 transfer RNAs (tRNAs) and 2 ribosomal RNAs (rRNAs). These RNAs are essential for translating protein-coding units within the mitochondria and for producing 13 protein subunits that make up 4 biochemical complexes. Mutations have been identified in the mitochondrial DNA of every kind of mitochondrial gene[23]. The fact that mitochondrial DNA is frequently linked to illness may be explained by a number of its characteristics. Since mitochondrial DNA lacks introns and mutates more often than nuclear DNA, a random mutation will typically affect a coding DNA sequence [24]. Furthermore, mitochondrial DNA is susceptible to oxygen free radicals produced by oxidative phosphorylation and lacks both protective histones and an efficient repair pathway. Due to the maternal inheritance of mitochondrial DNA and its non-recombination, mutations progress successively via maternal lineages. Each cell has many mitochondria, and each mitochondrion has two to ten DNA molecules. Thus, inside the same cell, mitochondrial DNA that is normal and mutant can

coexist. This state, called heteroplasmy, permits the persistence of a mutation that would otherwise be fatal as shown in figure 2 [25].

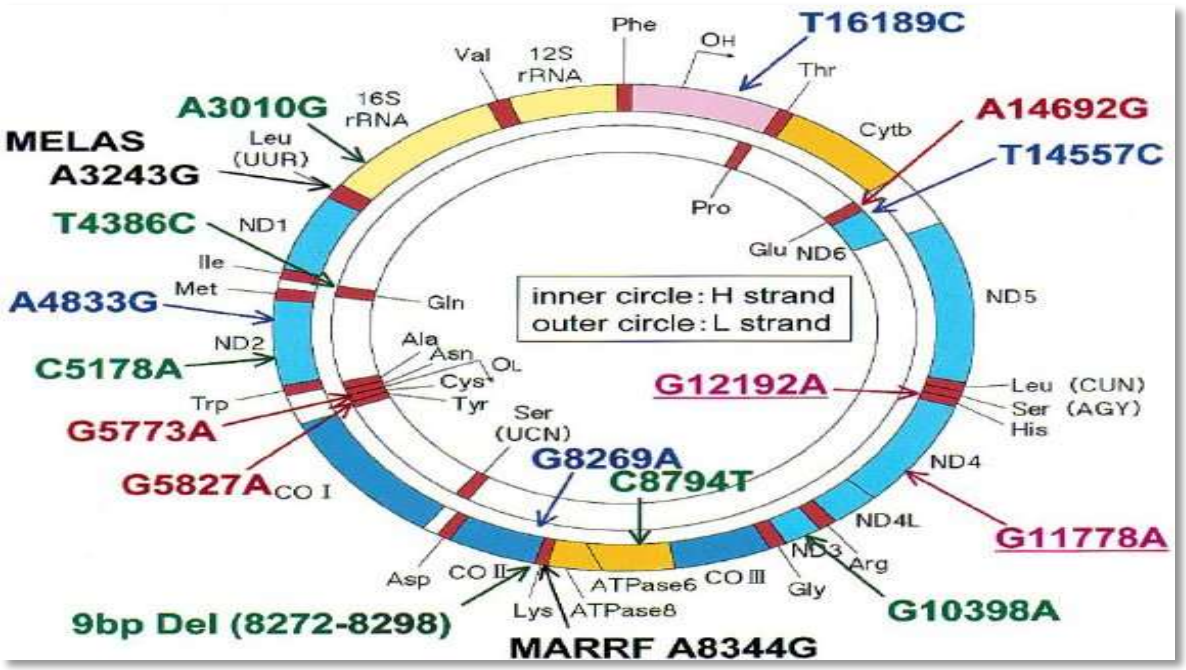

Figure 1. The complete genome of human mitochondrial DNA (mtDNA). Mitochondrial DNA (mtDNA) is composed of 16,569 base pairs (bps) that are sequentially numbered using the system established by Stephen, E. D. et al. [53].

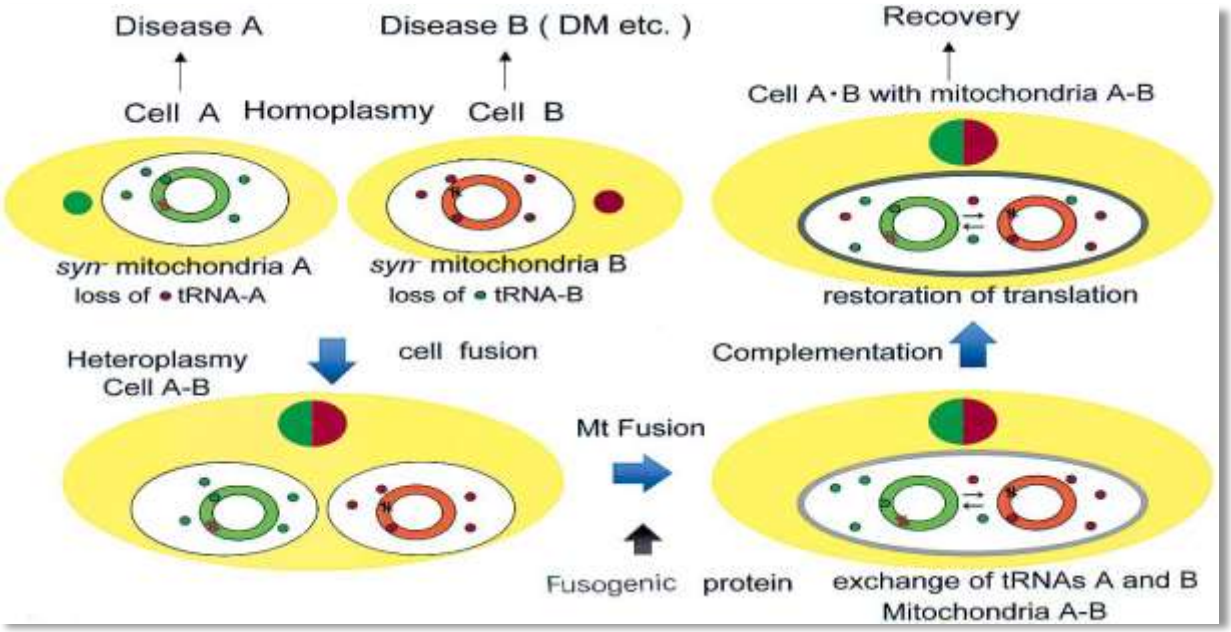

Figure 2. Genetic changes presence of several types of genetic material inside mitochondria, merging of mitochondria and the combination of genetic material from different mitochondria, with separate mtDNAs, as well as heterokaryon, with diverse nDNAs. The fusogenic protein merges mitochondria A and B, resulting in the formation of mitochondria A-B at the bottom right. Upper right: The complementation of two distinct syn mutations is achieved by replacing the remaining wild type tRNAs A and B. Cellular functionality been restored. To provide more precise examples of disorders [16].

3. Mitochondrial DNA disease

The discovery of disease-causing mutations in mitochondrial DNA (mtDNA) was initially documented in 1988. Since then, over 300 pathogenic mtDNA mutations have been identified and characterized [26]. Mitochondrial DNA (mtDNA) illness exhibits a highly diverse phenotype and can manifest at any stage of life [22]. The primary causative factor behind most mitochondrial cytopathies at the cellular level is believed to be a persistent state of energy deficiency. Cells with insufficient ATP production through oxidative phosphorylation (OXPHOS) may redirect pyruvate towards lactate production as a means to generate more ATP, leading to the development of systemic lactic acidosis [27]. Most of these patients will not exhibit any clinical signs since the mutation of mtDNA minimal amounts of variation in heteroplasmy. Conversely, the mutation causes deafness exclusively in individuals who receive a specific antibiotic [28]. Most main rearrangements of mitochondrial DNA (mtDNA) include massive loss amounts. More than 120 unique mitochondrial with different illnesses [29]. A significant fraction of mitochondrial DNA (mtDNA) deletions take place in certain areas of the genome that are bordered by tandem repeat sequences. These deletions are most likely created through the repair of damaged mtDNA [30]. The majority of mitochondrial DNA (mtDNA) deletions are rare occurrences and are not inherited by offspring. The etiology of mtDNA deletion illnesses relies on the distribution of tissues affected, and all documented deletions are consistently heteroplasmic. Mutations in the genome have been connected with three main medical signs: Pearson's syndrome, Kearns-Sayre syndrome (KSS), and chronic progressive external ophthalmoplegia (CPEO). Pearson coefficient syndrome presents in infancy sideroblastic anemia, pancytopenia, and exocrine pancreatic failure [31]. It is believed that harmful mutations in the RNA genes of mtDNA lead to a disruption in the production of mitochondrial proteins as a whole, whereas abnormalities in the genes that encode proteins impact particular complexes in the respiratory chain. Over 50% of disease-associated point mutations are found in mt-tRNA genes, even though these genes make up only approximately 5% of the mitochondrial genome. A frequently observed heteroplasmic disease-causing point mutation in The pathogenic characteristics might lead to temporary cerebral ischemia, resulting in stroke-like events [32].

Malfunctions in mitochondrial activity of enzymes have been found in the endothelium and smooth muscle of the leptomeningeal and cortical blood arteries in the brain [33]. This mutation has also been linked to involvement in constipation and gastric discomfort, which are the most frequently observed symptoms. Another frequently seen mutation in mtDNA that is linked to illness is the substitution of an A nucleotide with a G nucleotide at position 8344 in the MT-TK gene [34]. This mutation is responsible for causing a condition known as myoclonic epilepsy with ragged red fibers (MERRF). Additional characteristics encompass sporadic encephalomyopathy, lack of coordination, severe headache, and cognitive decline. MERRF is a degenerative illness of the nervous system that often begins in childhood or early adulthood. It is characterized by the loss of muscle mass in the proximal regions of the body and the presence of neurological symptoms such as epilepsy, cerebellar ataxia, and optic atrophy [35]. Nonneurological signs include re-entrant atrioventricular tachycardias and multiple identical lipomas.

4. Histopathological features of mtDNA disease

A multidisciplinary strategy is essential for identifying mitochondrial disease. This entails integrating data from medical, histochemical, and physiological investigations to emphasize molecular genetic testing [36]. The process is led by reasonable diagnostic algorithms. Diagnostic procedures in the laboratory often include examining clinically significant tissue, including skeletal muscle. Nevertheless, the heart or the liver's tissues may also be appropriate. Several individuals have histological and histochemical changes indicating a deficiency in oxidative phosphorylation (OXPHOS) [37]. The provided illustrations (a-e) demonstrate the histological and histochemical evaluation of consecutive, transversely-oriented slices of biopsy tissue from the vastus lateralis muscle of a patient with a single, extensive deletion in their mtDNA. These illustrations provide valuable insights for diagnosing mtDNA-related diseases in a laboratory setting. The sections showcase two fibers that have been dyed or reacted for the following purposes: The following techniques were used to analyze the muscle samples: Hematoxylin and eosin termed as (H&E) staining used to analyze the general muscle architecture. Irregular fibers with a grainy look and dark-staining edges were detected. The modified Gomori trichrome stain was used to selectively emphasize the aberrant fibers known as classical ragged-red muscular fibers. COX histochemistry was performed to evaluate the lack of cytochrome oxidase (COX) in these fibers. The extent of insufficiency differed among the fibers. The

succinate dehydrogenase (SDH) reaction was used to identify the increase in mitochondrial function in the subsarcolemmal area. Sequential COX/SDH histochemistry was conducted to emphasize the COX-deficient fibers that nonetheless showed SDH activity. Mutations in mitochondrial DNA (mtDNA) and nuclear-encoded proteins related to cytochrome c oxidase (COX) assembly may lead to a total and extensive reduction in COX activity as shown in figure 3. This is shown in (f) by testing COX activity alone and in (g) by examining successive COX-succinate dehydrogenase (SDH) activities. COX deficiency has a distinct 'mosaic' distribution pattern that might vary based on the particular mutations. This is shown using consecutive COX/SDH histochemistry in muscle samples from individuals with either a single, large-scale deletion in mtDNA or a mutation in mitochondrial transfer RNA (tRNA) [38].

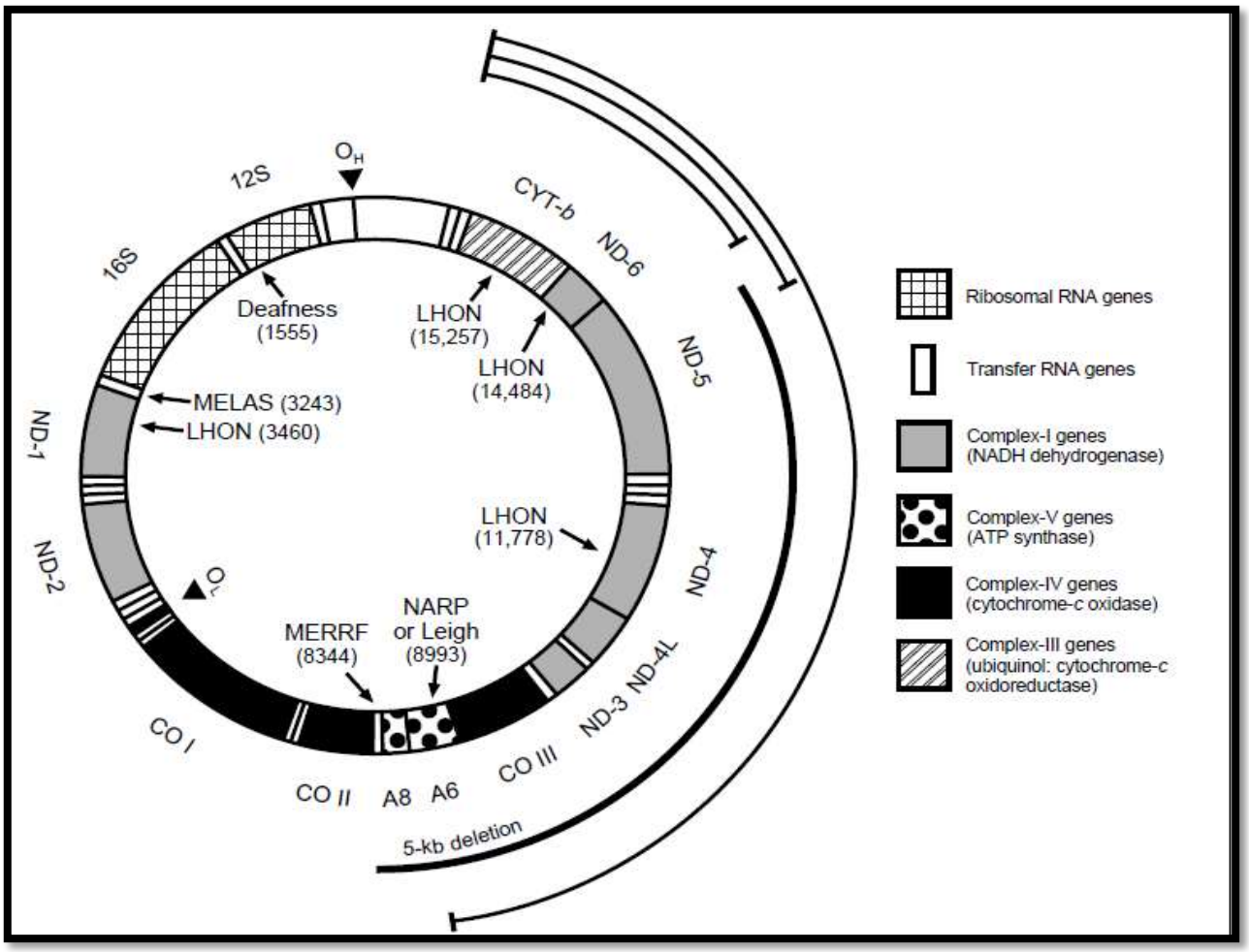

Figure 3. Schematic representation of DNA and the prevailing pathogenetic mutations associated with it [54].

5. Typical Characteristics of Mitochondrial Encephalomyopathy

Before 1988, the first abnormal mitochondrial DNA was identified, leading to the preliminary classification of various diseases as mitochondrial disorders based on irregular morphological or biochemical properties of mitochondria or a pattern of maternal inheritance. The first definitive evidence connecting mitochondrial DNA to a medical condition came through two results: the detection of notable changes in mitochondrial DNA in people with mitochondrial myopathies and the finding of a missense mutation in mitochondrial DNA in individuals with Leber's hereditary optic neuropathy. In the subsequent years, scientists discovered the cellular genetic basis of common mitochondrial encephalomyopathies [39].

6. Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes (MELAS) Syndrome

MELAS syndrome is characterized by attacks, stroke-like episodes, subacute dysfunction of the brain, cerebral structural alterations, and many clinical and analytical problems. The condition is inherited via the maternal line however it may not manifest in relatives who do not display all the obvious signs. 80% of patients have a point mutation at nucleotide position 3243 in the tRNA Leu (UUR) gene [40]. Additional mutations were discovered in this gene, indicating it is often targeted by pathogenic variants. The mutation at nucleotide site 3243 is linked to several phenotypic consequences, including nondeletion chronic progressive ophthalmoplegia, myopathy, which is deafness, type 2 diabetes, and dystonia [41].

7. The importance of mtDNA haplotypes

The significance of mitochondrial DNA (mtDNA) haplotypes During the migration of human beings from Africa, they have acquired unique genetic variants in their mtDNA (mitochondrial DNA) compared to our original 'mitochondrial Eve'. This has led to the development of several haplotypes that are exclusive to different ethnic groups [42]. There is a suggestion that various mtDNA haplotypes can alter oxidative phosphorylation, which in turn affects the general physiology of individuals and makes them more susceptible to or protected against specific illnesses. Reportedly, mtDNA haplotypes are said to impact functional traits such as intelligence quotient (IQ), spermatozoa swiftness, and tolerance to cold temperatures. Cardiomyopathy, Alzheimer's disease, dementia with Lewy bodies, and multiple sclerosis have been linked to certain mtDNA haplotypes. In addition, individuals diagnosed with LHON and specific mtDNA haplogroups are more prone to acquiring blindness. However, there is no confirmed association between the varying phenotypic manifestation of MELAS-3243 and mtDNA haplotypes. However, a recent investigation conducted across many centers, looking back at past cases of patients with MELAS and the A3243G mutation, was unable to verify a previously suggested link between a polymorphic variation (A12308G) and a higher likelihood of stroke. Undoubtedly, there is still a significant amount of study that has to be undertaken in order to more precisely determine the disease-causing impact of homoplasmic mutations and the regulatory influence of haplotypes on both health and illness [43].

8. Systemic Effects of Mitochondrial DNA Mutation

Most organs in the body depend on oxidative metabolism and are thus vulnerable to the effects of mitochondrial-DNA disorders. Patients sometimes first seek medical help because of systemic indications. Nonneurologic signs of mitochondrial DNA abnormalities are not widely acknowledged [44]. Ophthalmologic signs are common and may impact several sections of the visual axis, such as the eyelids, cornea, extraocular muscles, and occipital brain. The main findings include drooping eyelids, paralysis of the eye muscles, damage to the optic nerve, changes in the retina's pigmentation, and problems in the visual field of the brain's cortex. Cardiac abnormalities such as cardiomyopathy, conduction abnormalities, cardiac block, Wolff-Parkinson-White syndrome, and hypertension are prevalent and may be dangerous [45].

9. Polyplasmy Heteroplasmy and homoplasmy

The quantity of mtDNA copies differs across tissues, ranging from a minimal amount in platelets to over 100,000 copies in the oocyte. Most tissues contain between 1000 and 10,000 molecules per cell. Multiple populations of mtDNA may coexist inside a cell, homoplasmy is when a single kind of mtDNA is present. Heteroplasmy rate is determined by the fraction of mutant mtDNA in respect to total mtDNA [14]. As the egg matures, the processes of blastocyst segmentation and mitotic segregation may result in varying levels of heteroplasmy, causing changes in the mitochondrial genotype between maternal cells and daughter cells. This may result in differences in mitochondrial genetic makeup among daughter cells and, subsequently, among other organs. mtDNA mutations are often heteroplasmic, resulting in tissues with a high mutation rate being most impacted [46].

10.Segregation

During growth, the nucleus conducts several replications, and the cytoplasm of the egg is split to form the blastocyst. In cytokinesis, the cytoplasm is divided, and the distribution of mitochondria within cell layers is random. The mitochondria replicate inside the cytoplasm, and each cell divides by mitosis, producing two daughter cells [47].

11.High rate of mutation

Several factors contribute to this phenomenon: the mtDNA repair system is less efficient than the nucleus, lacks histone protein protection, and is situated close to the respiration chain, which generates a large number of reactive oxygen species

(ROS) that can harm the genome of mitochondria due to a condition known as oxidative stress. During replication, mitochondrial DNA is particularly vulnerable because to its prolonged exposure in a single stranded state, making it more susceptible to radical assaults. Multiple investigations have shown that mitochondrial mutations increase as individuals age [48].

12. Various Mutation Types

About 20% of mitochondrial disorders are caused by defects that impact mtDNA. Despite encoding a limited number of genes, mutations in this DNA are frequent. Most of these mtDNA anomalies are heteroplasmic and inherited maternally; however, they may arise as de novo mutations in certain instances. Primary changes in mtDNA linked to mitochondrial illnesses include point mutations, deletions, insertions, and depletion, which are associated with mutations in nuclear genes necessary for mtDNA upkeep [49].

13. Diseases

With more 150 deleterious mtDNA mutations, the offspring of an individual with a point mutation are not at risk. On the other hand, there is a significant risk [50]. Mitochondrial mutations are varied and may develop at any point in life, affecting all bodily tissues from prenatal stages to old age as shown in figure 4. They are mentioned in relation to a certain group of symptoms or clinical or paraclinical signs. Diagnosing the problem is challenging due to the dual genetic control (mitochondrial and nuclear) of the OXPHOS system. Many diseases cannot be conclusively diagnosed just based on the absence of a mtDNA mutation in a blood sample. A tissue sample is needed to identify histological abnormalities associated with a biochemical deficit in the respiratory chain, as well as mutations or instability in mtDNA, to direct genetic analysis as shown in figure 5 [51].

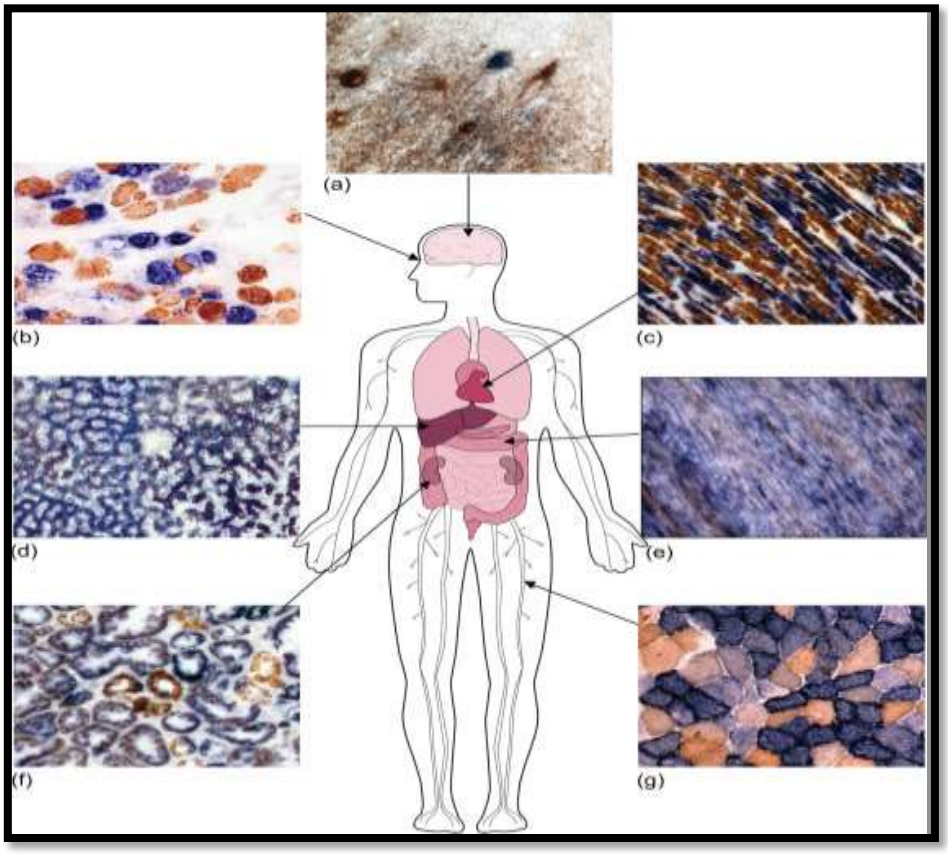

Figure 4. Tissues that are frequently impacted by diseases related to mitochondrial DNA. Letters a through g Sequential COX/SDH histochemistry was conducted on parts of different tissues from humans, such as the cerebellum, extraocular skeletal muscle, the heart, the liver, the soft muscle of the colon, kidney, and quadriceps muscles of the skeleton from patients with primary mtDNA abnormalities. Cells with normal cytochrome c oxidase (COX) activity will become brown during COX histochemistry. Cells without COX activity become blue during sequential succinate dehydrogenase (SDH) histology [55].

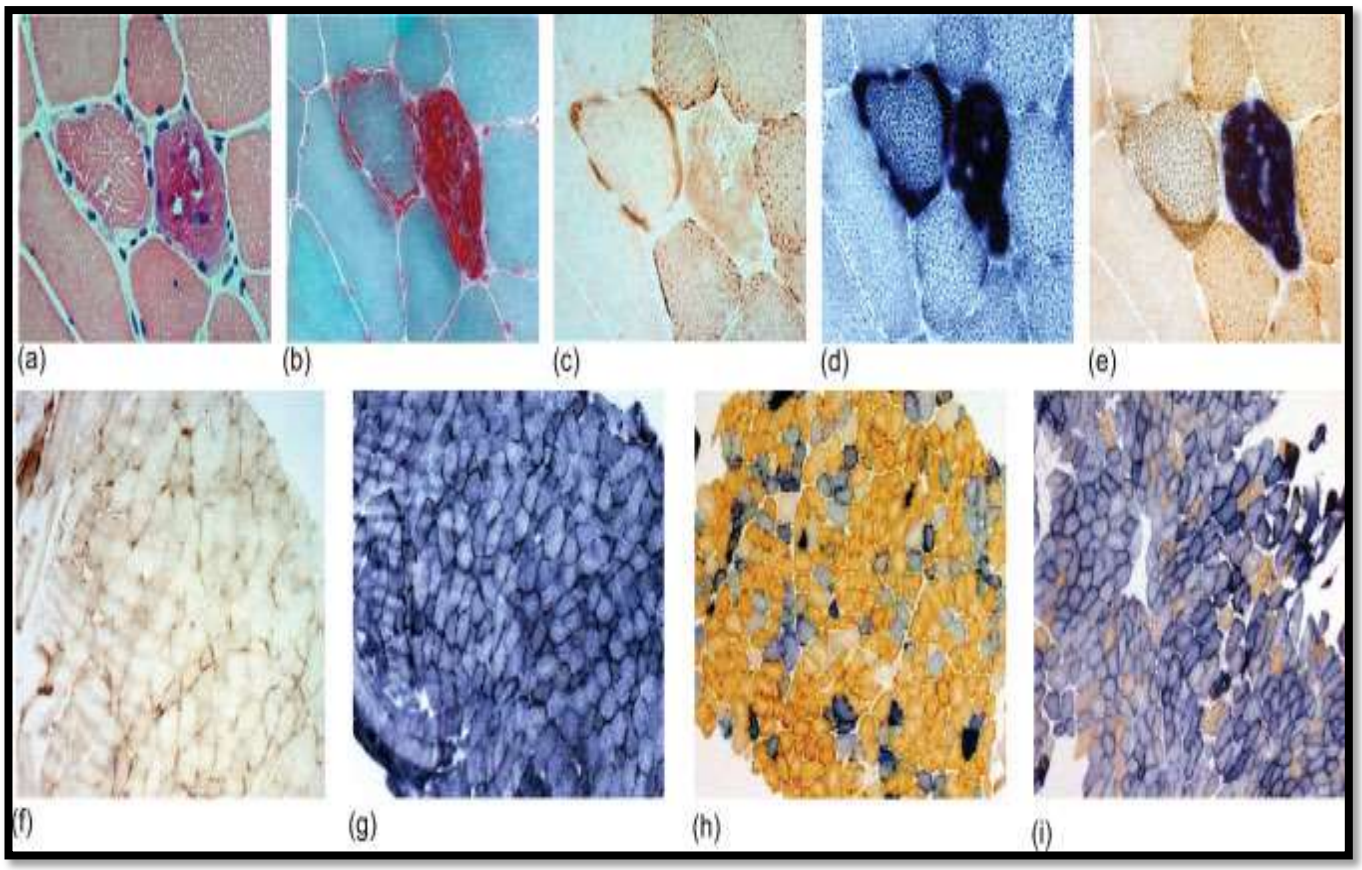

Figure 5. Histopathological abnormalities that are often detected in primary diseases linked to mitochondrial DNA (mtDNA).

14.Investigation of tissues

Studying tissues is essential for identifying mitochondrial myopathies. Anatomopathological research confirms the presence of certain abnormalities. Nevertheless, their lack, typical of young individuals, does not exclude the possibility of diagnosis [52].

15. Conclusions

Two key characteristics of mitochondrial DNA (mtDNA) are crucial for comprehending MM: maternal-only inheritance and heteroplasmy, which refers to the varying amount of mutant mtDNA in different cell types. The variation in the mitochondrial genome complicates the diagnosis of MM. Mitochondrial malfunction is involved in three key categories of illness: primary mitochondrial disease, neurodegeneration, and cancer. Additionally, it contributes to the deterioration of tissue integrity as individuals age. Despite considerable advancements in our comprehension of the involvement of mitochondria in these diseases within the last twenty years, some essential inquiries persist. Patients with primary mtDNA illness now lack an effective treatment, and the growing number of documented nuclear and mtDNA mutations, together with the expanding range of clinical symptoms, present challenges in diagnosing the condition. The biochemical and molecular mechanisms associated with mitochondrial abnormalities in neurodegeneration, ageing, and cancer have not yet been determined. Distinguishing between cause and effect in these conditions is an ongoing and difficult task. It is imperative that we enhance our understanding of the molecular pathways implicated and formulate new treatment approaches.

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